Cellular tools to study brain diseases affecting synaptic transmission

Grant Award Details

Cellular tools to study brain diseases affecting synaptic transmission

Grant Type: Tools and Technologies II

Grant Number: RT2-02061

Project Objective: The goal of this proposal is to develop cellular tools for studying neurological brain diseases affecting synaptic function. Specifically, the PI will develop TF-based fibroblast-induced neuronal models for neurodevelopmental diseases.

Investigator:

Name:	Marius Wernig
Institution:	Stanford University
Type:	PI

Disease Focus: Autism, Neurological Disorders, Pediatrics, Rett's Syndrome

Human Stem Cell Use: Embryonic Stem Cell, iPS Cell

Cell Line Generation: Embryonic Stem Cell, iPS Cell

Award Value: $1,664,382

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Cellular tools to study brain diseases affecting synaptic transmission

Public Abstract:

There is a group of brain diseases that are caused by functional abnormalities. The brains of patients afflicted with these diseases which include autism spectrum disorders, schizophrenia, depression, and mania and other psychiatric diseases have a normal appearance and show no structural changes. Neurons, the cellular units of the brain, function by making connections (or synapses) with each other and exchanging information in form of electric activity. Thus, it is believed that in those diseases many of these connections are not working properly. However, using current technology, there is no way to investigate individual neuronal synapses in the human brain. This is because it is not ethical to biopsy the brain of a living person if it is not for the direct benefit to the patient. Therefore, scientists cannot study synaptic function in psychiatric diseases. Because of the limited knowledge about the functional consequences in the affected brains, there is no cure for these diseases and the few existing therapies are often associated with severe side effects and cannot restore the normal function of the brain. Therefore, it is of great importance to better study the disease processes. A better knowledge on what the defects are on the cellular level will enable us then in a second step to test existing drugs and measure its effect or screen for new therapeutic drugs that can improve the process and hopefully also the disease symptoms.

This proposal aims to develop a technology to overcome this limitation and ultimately provide neurons directly derived from affected patients. This will uniquely allow the study functional neuronal aspects in the patients' own neurons without the need to extract neurons from the brain. Our proposal has two steps, that we want to undertake in parallel with mouse and human cells. First, we want to find ways to optimally generate neurons from skin fibroblasts. Naturally, these artificial neurons will have to exhibit all functional properties that the neurons from the brain have. This includes their ability to form functional connections with each other that serve to exchange information between two cells. In the second step, we will generate such neuronal cells from a genetic form of a psychiatric disease and evaluate whether these cultured neuronal cells indeed exhibit changes in their functional behavior such as the formation of fewer connections or a decreased probability to activate a connection and thus limit the disease cells to communicate with other cells.

Statement of Benefit to California:	Our proposed research is to develop a cellular tool which will enable the research community to study human brain diseases that are caused by improperly functioning connections between brain cells rather than structural abnormalities of the brain such as degeneration of neurons or developmental abnormalities. These diseases, which are typically classified as psychiatric diseases, include schizophrenia, bipolar diseases (depression, mania) autism spectrum disorders, and others. There are many people in California and world-wide that suffer from these mentally debilitating diseases. Therefore, there is a great need to develop therapies for these diseases. However, currently drug development is largely restricted to animal models and very often drug candidates that are successful in e.g. rodent animals can not be applied to human. It would thus be much better to possess a model that reflects the human disease much closer, ideally using human cells. We have experimental evidence that we can develop such a model. In particular, we will convert skin cells from patients suffering from psychiatric diseases into stem cells that are "pluripotent", which means they can differentiate into all cell types of the body including neurons. We want to explore whether these patient-derived neurons still contain the disease features that the neurons have in the brain. If we could indeed capture the disease in these cells, our technology would have a major impact on future work in this area. We believe that this approach could be applied to many neurological diseases including neurodegenerative diseases. Our technology would not only provide a unique experimental basis to begin to understand how these diseases work, but it would allow to then interfere with the identified cellular abnormalities which would secondarily result in the development of new drugs that can counteract the diseases and would hopefully also work for the patients themselves. Therefore, all those Californians that suffer from one of the above mentioned diseases will benefit from our research project, if it is successful.

Source URL: https://www.cirm.ca.gov/our-progress/awards/cellular-tools-study-brain-diseases-affecting-synaptic-transmission